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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,396	07/10/2001	Keith D. Allen	R-359	9463

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,396	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,13-16,30-32,34-41,47 and 48* is/are pending in the application.

4a) Of the above claim(s) *1-4,13-16,30-32,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-41,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07/10/2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed 06/25/2004 has been entered. Claims 42-46 have been cancelled. Claims 36 and 47 have been amended. Claims 1-4, 13-16, 30-32 and 34-35 have been withdrawn. Claims 1-4, 13-16, 30-32, 36-41, 47 and 48 are pending and claims 36-41,47 and 48 are under consideration in the instant office action.

It is noted that the text of withdrawn claims should appear in the listing of the claims. Thus the amendments to the claims are not consistent with 37 CFR 1.121. Future amendments to the claims should include the text of all withdrawn claims or indicate their cancellation.

This application contains claims 1-4, 13-16, 30-32 and 34-35 drawn to an invention nonelected with traverse the election dated 02/10/2003. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 101/112-1st paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 36-41,47 and 48 as lacking utility as set forth on pages 3-5 of the previous office action mailed 11/06/2003 is maintained. Applicant's arguments have been thoroughly considered and are not found to be persuasive. The rejection is maintained for reasons of record.

1) Applicant argues that the claimed transgenic mouse exhibits a number of specific phenotypes resulting from disruption of the glucocorticoid-induced receptor gene. Applicant argues that the phenotypes, including hyperactivity, reduced anxiety, decreased propensity toward behavioral despair and decreased propensity toward depression make the mouse an in vivo model for conditions or disorders related to these phenotypes such as hyperactivity, anxiety and depression. Applicant asserts that this utility is specific to the claimed mouse because it is a specific phenotype exhibited by the mouse as a result of the disruption.

In response, there is no known disorder on the record that is characterized by reduced anxiety, decreased propensity toward behavioral despair or decreased propensity toward depression. Furthermore, there is no evidence on the record that the glucocorticoid-induced receptor even has a role in hyperactivity, anxiety or depression. There is no evidence on the record that the disclosed results in the open field test (pages 53-54) are due to reduced anxiety, decreased propensity toward behavioral despair or decreased propensity toward depression (see below). Applicant argues that the claimed phenotypes are specific to the claimed mouse; however, a phenotype specific to the mouse does not render the utility of the mouse specific. The claimed phenotypes are not specific to any disease or disorder such that there would be a specific use for the mice. Furthermore, having an increased propensity for a disease does not necessarily make a mouse a model for that disease. Merely having an increased likelihood of exhibiting a disease state does not indicate that a mouse will ever exhibit or have the disease.

2) Applicant argues further that the claimed mice have substantial and credible utility because compounds identified using the mice will have therapeutic value as modulators of

phenotypes resulting from the claimed disruption (page 5, 2nd paragraph). Applicant argues that the mice represent a valuable method for determining the function of genes.

In response, it is not apparent what utility a compound that modulates decreased propensity for depression or behavioral despair would be. With respect to these claimed phenotypes, the only assay the claimed mouse could be used for over the use of a wild-type mouse would be in identifying an agent that reverses the phenotypes of decreased pain sensitivity, or increased pain sensitivity. One could argue that use of the claimed mouse to identify compounds that modulate the claimed phenotypes offers no utility over wild-type because the glucocorticoid-induced receptor gene has no correlation to diseases associated with the phenotypes and therefore, an agent that increases propensity to behavioral despair or depression would have the same effect on a wild-type mouse and could have been identified using the wild-type mouse. Furthermore, there is no apparent utility for an agent that increases propensity for behavioral despair or depression.

Furthermore, the mouse described in the specification exhibit increased distance traveled in the open field test and less time immobile in the tail suspension test. As set forth in the specification, these phenotypes or results **may** be indicative of increased hyperactivity or decreased anxiety (page 53, lines 26-28) or **may** be indicative of decreased propensity for behavior despair and/or depression (page 54, lines 5-7). Without additional experimentation, based on the evidence of record, a definitive correlation between the claimed disruption, hyperactivity, anxiety, or depression cannot be made. Therefore, the claimed utility is not substantial because it requires further experimentation.

Applicant's argument that the claimed mice are a tool for further research is not persuasive in arguing that the claimed mouse has substantial utility because, as set forth in the utility guidelines (see REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS; repeated from http://www.uspto.gov/web/menu/utility.pdf), basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved." Does not constitute a substantial utility.

3) Applicant argues that there is no requirement for a correlation between disruption of the glucocorticoid-induced receptor gene and a disease or disorder (page 6, paragraph 1).

In response, the specification fails to demonstrate the etiology of the claimed hyperactivity, reduced anxiety, decreased propensity toward behavioral despair or decreased propensity toward depression or to demonstrate adequately that the response of the mouse in the open field test or the tail flick test is due to hyperactivity, reduced anxiety, decreased propensity toward behavioral despair or decreased propensity toward depression and not to some other physiological or neurological disorder, or non-specific difference in a mouse's behavioral disposition that results from genetic background differences. For example, perhaps the claimed mice are generally more energetic and explorative or more easily irritated and these character traits are not a result of the genetic disruption, per se. A child who, when left free, prefers to roam rather than sit or hide in a corner would not be necessarily labeled as hyperactive. A child who is more easily irritated by and reactive to a flick of his ear is not necessarily a child who has less of a propensity toward depression. While these behaviors are potential indicators of a disease state, they are not definitive and require further experimentation to verify a correlation

(refer to Gass). Furthermore, the specification supports that the claimed phenotypes may result from a more general phenomenon of genetic background rather than specific disruption of the glucocorticoid-induced receptor gene as it teaches that mice generated through backcrossing the F1 generation exhibited the claimed phenotypes whereas those made by intercrossing the F1 generation did not exhibit the claimed phenotypes. Hence, mice of one genetic background, while comprising the claimed disruption, do not exhibit the claimed phenotypes while mice of a different genetic background do exhibit the claimed phenotypes. Logically, one might be inclined to conclude that the phenotypic differences in the mice are due to genetic background and not to disruption of the glucocorticoid-induced receptor gene (refer to the explanation on pages 7-8 of the previous office action; refer also to Crabbe, 1999; Yoshikawa, 2002; Liu, 2001; Mayorga, 2001).

As such, one would not know how to use a compound that ameliorates the response of the claimed mice in the open field test or tail flick test because it would not be known what the compound is affecting. Better characterization of the glucocorticoid-induced receptor function that correlates the glucocorticoid-induced receptor gene to hyperactivity, anxiety or depression, a link between the glucocorticoid-induced receptor gene and a disease or condition, and further testing more definitively correlating the gene disruption specifically to the claimed phenotypes per se, would all provide a stronger correlation between disruption of the glucocorticoid-induced receptor and one of the claimed phenotypes, allowing for credible and specific utility of the claimed mouse. Applicant asserts the utility of the mouse is substantial; however, additional experimentation would be required to determine the usefulness of the claimed mice

because it must be determined whether a compound that ameliorates the results exhibited by the mice in the open field test or tail flick test is affecting hyperactivity, anxiety or depression and not some other unidentified characteristic of the mouse that affects its performance in these tests. As set forth by the utility guidelines above, utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

4) Applicant argues that mice displaying phenotype of reduced anxiety and decreased propensity toward depression and/or behavioral despair are useful as models of antagonism of the disrupted glucocorticoid-induced receptor gene and would provide an in vivo model for treating related condition of anxiety and depression. Applicant argues that the mice would be useful to compare the responses of an agent in a knockout or wild-type mouse or to determine whether agents would act additively or synergistically to treat disorders related to the claimed phenotypes (page 6, 2nd paragraph).

In response, the usefulness of the claimed mice as argued by Applicant on page 6, paragraph 2, is not apparent. A wild-type mouse can be treated with a putative agent and the effect of the agent can be assessed in the open field test or tail flick test independent of the claimed mouse. The claimed mouse is not needed for comparison to determine that the agent causes increased distance traveled in the open field test, for example. The claimed mouse is not needed to determine an additive or synergistic effect between two agents.

5) Applicant argues that a mouse does not necessarily have to exactly mimic a disorder such as depression to be useful in screening for therapeutics. Applicant argues

accordingly against the teachings of Gass (2001) as Gass teaches that mice are not useful unless it is demonstrated that they specifically reflect human disease.

In response, Applicant's argument is not applicable to Gass b/c Gass does not require that a model exactly mimic, only that it be specifically reflective of a disease to have a use. Accordingly, the claimed invention fails to have a patentable utility not because it doe not exactly mimic human depression but because the asserted utility is not specific or substantial as set forth above.

6) Applicant argues that irrespective of the utility of the claimed phenotypes of decreased propensity toward behavioral despair and/or depression, the claimed mice have utility in investigating agents capable of modulating hyperactivity. Applicant argues that the other phenotypes exhibited by the mice do not negate the hyperactivity phenotype and the usefulness associated with that phenotype.

In response, all arguments set forth above apply to the claimed mouse exhibiting the claimed hyperactivity phenotype. For example, there is no correlation between the glucocorticoid-induced receptor gene and hyperactivity. There is no definitive correlation between the performance of the mouse in the open field test, hyperactivity, and the claimed phenotype. Therefore, the utility rejection set forth above applies to the claimed mouse with respect to each of the claimed phenotypes.

Without additional experimentation or correlation between the function of the glucocorticoid receptor gene and a disease, one would not know what to do with a compound that affects the performance of the claimed mouse in the open field test or in the tail flick test. Absent further characterization of the mice or the glucocorticoid-induced receptor gene, it cannot be determined that a compound that affects the claimed

phenotypes would have any use. Thus, neither the claimed mice nor the methods of making the mice have utility.

Enablement

Claims 36-41,47 and 48 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In addition to the above enablement rejection, claims 36-41,47 and 48 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Aspects of the previous rejection set forth on pages 6-10 of the previous office action mailed 11/06/2003 are maintained as set forth below.

1) The aspect of the rejection with respect to the specification failing to enable the claimed mouse comprising a disruption in any glucocorticoid-induced receptor gene is withdrawn in light of Applicant's amendments to the claims.

2) The aspect of the enablement rejection on the grounds that the specification fails to enable the claimed mice comprising a disruption in the glucocorticoid-induced receptor gene wherein the mouse is of any genetic background is maintained for reasons of record.

Applicant has argued that it was chosen to backcross to the C57Bl/6 strain in making the claimed mice because this strain is widely used in the art because of the consistent and predictable behavior in the described tests (pages 8, 3rd paragraph). Applicant argues that the N0 (not backcrossed to the C57Bl/6 strain) may mask real phenotypes that would be revealed after backcrossing and that this is likely the case for the glucocorticoid-induced receptor knockout mice of the instant invention.

In response, the "N1" generation has been backcrossed to the C57Bl/6 strain that, accordingly to applicant, is more consistent in its behavior using the described behavioral tests and backcrossing to said strain would reveal any "real" phenotypes that are "masked" in the "N0" generation (which was not backcrossed). This argument is not persuasive because it fails to overcome the rejection based on the failure of the specification to enable making the claimed mouse wherein the mouse is of any genetic background. It is evident based on the teachings in the specification that the mice must be carefully constructed with respect to genetic background to obtain the claimed phenotypes. The specification does not teach any other means of obtaining the claimed phenotypes in the claimed mice other than by making the mice according to the methods set forth on page 53 with respect to generating the F1N1 generation and the associated genetic background. Therefore the specification is not enabling for any other genetic background than that which results from backcrossing the F1N0 to C57Bl/6 as set forth in the specification.

3-5) The aspects of the enablement rejection with respect to the use of the term "murine", the breadth of the claims with respect to chimeric mice, and breadth of the

claims encompassing heterozygous mice with no phenotype, are withdrawn in light of Applicant's amendments to the specification.

Written Description

The rejection of claims 36-41,47 and 48 under 35 U.S.C. 112 for lacking written description is withdrawn in light of the amendments to the claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio
Examiner
Art Unit 1632

Joe Woitach
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